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Metastasectomy for Recurrent Stage IV Melanoma

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Background and Objectives: Many patients undergoing complete surgical resection of distant metastatic melanoma (American Joint Committee on Cancer [AJCC] stage IV) develop recurrent disease. We examined whether a second metastasectomy could prolong the survival of patients with recurrent stage IV melanoma.

Design and Patients: Retrospective review of our 8,750-patient melanoma database identified 211 patients who were rendered clinically free of disease by surgical resection of stage IV metastases during the 24-year study period (January 1971 through December 1995). Our study population comprised the 131 patients who developed recurrent stage IV disease and were followed for at least 24 months or until death.

Results: The median disease-free interval prior to recurrent stage IV disease was 8 months (range 0.6–91.8 months). There were 131 tumor-involved anatomic sites; the median number was one (range 1–3). Of these sites, 71 (54.2%) were soft tissue, 35 (26.7%) were pulmonary, 28 (21.4%) were gastrointestinal, 23 (17.6%) were cerebral, 13 (9.9%) were skeletal, and 2 (1.5%) were gynecologic. Median survival following treatment for recurrent stage IV melanoma was 18.2 months after complete metastasectomy, compared with 12.5 months or 5.9 months after a palliative surgical procedure or nonsurgical management, respectively. The 5-year survival rate was 20.0% (8/40) for patients in the complete surgical metastasectomy group, compared with 7.0% (3/43) and 2.1% (1/48) for those in the palliative surgical and nonsurgical groups, respectively. By multivariate analysis, the two most important prognostic factors for survival following diagnosis of recurrent stage IV melanoma were a prolonged disease-free interval to recurrence ($P = 0.0001$) and complete surgical metastasectomy of the recurrence ($P = 0.0001$).

Conclusions: Metastasectomy can prolong the survival of patients with recurrent stage IV melanoma if all clinically evident tumor can be resected. *J. Surg. Oncol. 1999;71:209–213.*

KEY WORDS: melanoma; metastasectomy; metastases; recurrence; survival

INTRODUCTION

Traditionally, melanoma metastatic to distant sites has been managed with either single-drug or multidrug chemotherapy regimens. However, complete response (CR) rates have been nominal (<5%) and the increase in median survival minimal [1,2]. Several investigators have re-examined the role of complete surgical metastasectomy for patients with American Joint Committee on

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Cancer (AJCC) stage IV melanoma. Recent series have demonstrated 5-year survival rates of 20–27% [3,4] following pulmonary metastasectomy and 28–41% [5–7] following complete resection of gastrointestinal metastases. In all of these reports, patients rendered disease-free by surgical resection fared significantly better than those undergoing incomplete surgical resection or nonoperative management.

Because complete surgical resection imparts a survival advantage to stage IV melanoma patients, we hypothesized that a second complete metastasectomy would benefit patients who developed recurrent stage IV melanoma.

MATERIALS AND METHODS

Using our computerized database of prospectively collected data for more than 8,750 patients with melanoma, we identified all patients who developed a recurrence following complete surgical resection of distant metastatic melanoma. The 24-year review period was January 1971 through December 1995. All patients met AJCC staging guidelines for distant subcutaneous, nonregional lymph node, and/or visceral metastases [8]. Patient charts were reviewed for the anatomic site(s) of initial stage IV metastases, the operative record of the initial metastasectomy, the site(s) of recurrent stage IV disease, and the type of management for recurrent stage IV melanoma.

Survival was defined as the time from first recurrence of stage IV disease to death or last follow-up. Estimated survival rates were computed using the Kaplan-Meier method. Univariate analyses were performed by the log-rank test for categorical factors and by the Cox proportional hazards model for continuous factors. Multivariate analysis was performed by the Cox proportional hazards model. All factors significant in univariate analysis were used in the multivariate analysis.

RESULTS

During the study period, 3,028 patients were treated for stage IV metastatic melanoma. Of these, 211 were rendered disease-free by surgical resection. Our study population comprised the 131 patients who subsequently developed recurrent stage IV melanoma and were followed for at least 24 months or until death. Patient demographics and the anatomic distribution of the initial stage IV tumor are summarized in Table I. In 122 (93.1%) patients, the initial metastasectomy involved only one anatomic site, although that site might harbor more than one tumor deposit. For example, a patient who underwent resection of multiple subcutaneous nodules was considered to have a *single* anatomic site of metastasis. The most common site of metastasectomy was soft tissue (51/131, or 38.9%), followed by lung (47/131, or 36.0%), gastrointestinal tract (20/131, or 15.3%), brain (13/131, or 9.9%), bone (4/131, or 3.0%), genitourinary tract (3/131, or 2.3%), and gynecologic sites (2/131, or 1.5%).

TABLE I. Patient Demographics and Characteristics of Initial Stage IV Tumor*

Factor	
Gender	
Number of males	81
Number of females	50
Age	
Median	47 years
Range	21–83 years
Number of tumor-involved anatomic sites	
Median	1
Range	1–2
Distribution of anatomic sites resected, N = 131 (%)	
Soft tissue	51 (38.9)
Lung	47 (35.9)
Gastrointestinal	20 (15.3)
Brain	13 (9.9)
Bone	4 (3.0)
Genitourinary	3 (2.3)
Gynecologic	2 (1.5)

*Soft tissue includes distant subcutaneous, nonregional lymph node and intramuscular metastases.

The median disease-free interval (DFI) between complete metastasectomy and first recurrence of stage IV metastatic melanoma was 8 months (range 0.6–91.8 months). Of the 131 patients with recurrent stage IV metastases, 40 (30.5%) underwent a second complete metastasectomy, 43 (32.8%) had an incomplete resection, and 48 (36.6%) were managed nonoperatively. A complete metastasectomy removed all macroscopically identifiable tumor, whereas an incomplete resection left nonresectable gross tumor. In general, patients managed nonoperatively had multiple brain or liver metastases and/or involvement of more than three anatomic sites.

Patient demographics and characteristics of the recurrent stage IV tumor are shown in Table II. Among patients undergoing either complete or partial surgical resection for recurrent disease, the most common operative site was soft tissue (51/83, or 61.5%), followed by lung (22/83, or 26.5%), gastrointestinal tract (19/83, or 22.9%), brain (12/83, or 14.5%), bone (5/83, or 6.0%), and gynecologic sites (2/83, or 2.4%). Fifty-nine (71.1%) patients underwent resection of only one anatomic site; 20 (24.1%) patients had two sites and 4 (4.8%) patients had three sites resected.

There were no procedure-related deaths among the 40 patients managed with a second complete metastasectomy. There was one death (2.3%) among the 43 patients managed with an incomplete resection. This patient had unilobar hepatic metastases on preoperative abdominal computed tomography. A planned hepatic lobectomy was aborted intraoperatively because of extensive bilobar hepatic involvement as well as extrahepatic disease. No resection was performed. Postoperatively, the patient de-

TABLE II. Patient Demographics and Characteristics of Recurrent Stage IV Tumor

	Type of management		
	Complete resection	Incomplete resection	Nonoperative
Total number of patients	40 (22 males)	43 (30 males)	48 (29 males)
Median time to recurrence	10.5 months	10.3 months	7.1 months
Median number of anatomic sites	1 (range 1–3)	1 (range 1–3)	1 (range 1–3)
Distribution of recurrent anatomic sites (%)			
Soft tissue[a]	25 (62.5)	26 (60.5)	20 (41.7)
Lung	7 (17.5)	15 (34.9)	13 (27.1)
Gastrointestinal	8 (20.0)	11 (25.6)	9 (18.8)
Brain	7 (17.5)	5 (11.6)	11 (22.9)
Bone	1 (2.5)	4 (9.3)	8 (16.7)
Gynecologic	0	2 (4.6)	0

[a]Distant subcutaneous, nonregional lymph node and intramuscular metastases.

veloped irreversible hepatorenal syndrome and expired within the month.

Median survival following first recurrence was 18.2 months for patients undergoing complete metastasectomy, compared with only 12.5 months and 5.9 months for those undergoing incomplete surgical resection and nonoperative interventions, respectively. The rate of 5-year survival was 20.0% (8/40) with complete metastasectomy, 7.0% (3/43) with incomplete surgical resection, and 2.1% (1/48) with nonsurgical management (Fig. 1). Univariate analysis demonstrated that complete or partial surgical resection of recurrent stage IV disease and a prolonged DFI prior to recurrence significantly prolonged the survival following recurrence. However, by multivariate analysis only a second complete metastasectomy and a prolonged DFI (≥8 months) remained statistically significant (Table III).

DISCUSSION

The traditional management of stage IV melanoma has been single-agent chemotherapy (dacarbazine) or multiagent chemotherapy (cisplatin, vincristine, and dacarbazine [CVD]; or cisplatin, carmustine, dacarbazine, and tamoxifen [Dartmouth protocol]). However, the complete response (CR) rate to single or multiple drugs is < 5% [1,2]. Biologic therapy using interleukin-2 has improved the CR rate modestly [9,10]. Recently, several investigators have reported 20–27% CR rates for a combination of biologic therapy (interleukin-2 and interferon

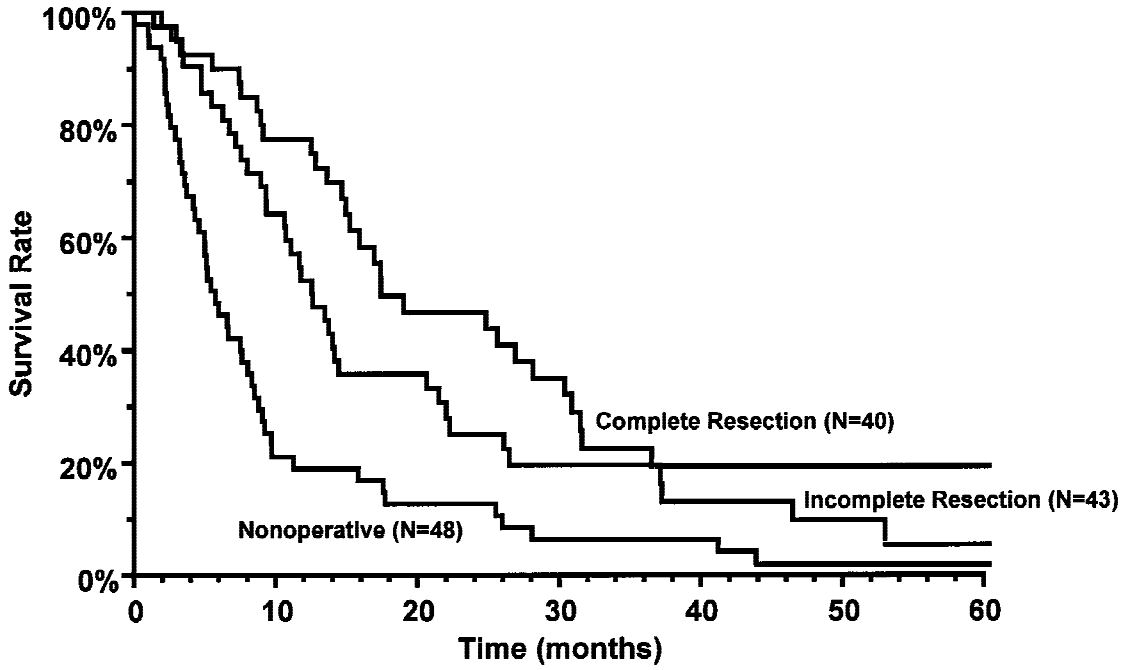

Fig. 1. Survival following complete surgical resection, incomplete surgical resection, or nonoperative treatment of stage IV melanoma recurring after an initial complete metastasectomy.

TABLE III. Univariate and Multivariate Survival Analysis*

Factor	Univariate *P* value	Multivariate *P* value
Age at stage IV diagnosis	0.7837	
Gender	0.9562	
Primary melanoma on extremity	0.9171	
Primary melanoma on trunk	0.1230	
Primary melanoma on head/neck	0.3780	
Primary melanoma in lymph nodes	0.1998	
Initial distant site (M1a, M1b)	0.4349	
Second distant site (M1a, M1b)	0.7704	
Intervening AJCC stage III disease	0.1868	
Number of anatomic sites of stage IV metastases	0.6431	
Treatment for recurrence (surgical, medical)	**0.0001**	**0.0001**
Disease status after treatment (NED, AWD)	**0.0001**	0.1632
Site of first recurrence (M1a, M1b)	0.0990	
Disease-free interval to Stage IV	0.9537	
Disease-free interval to first recurrence	**0.0001**	**0.0001**

*M1a, soft-tissue or lymph node metastases; M1b, visceral metastases; NED, no evidence of disease; AWD, alive with disease.

alfa-2b) and chemotherapy [11–16], but the durability of this response is not yet known.

Because of the poor overall response to chemotherapy, numerous investigators have advocated an aggressive surgical approach that attempts to excise all gross tumor [3–7,17,18]. Prolonged 5-year survival rates have been demonstrated following complete resection of metastases in soft tissue [17,18], lungs [3,4], and gastrointestinal tract [5–7]. In our present study, the 5-year survival rate following recurrence of stage IV melanoma was 21% for the 40 patients who underwent a second complete metastasectomy. This high percentage reflects careful selection of surgical candidates. Patients with disseminated cerebral or hepatic metastases were treated with radiation therapy and/or chemotherapy instead of surgery, whereas patients with metastases in a single anatomic site usually underwent surgical resection. However, our group and others have found that even patients with multiple pulmonary nodules can benefit from aggressive surgical resection [3,4] if these patients can be rendered disease-free via a thoracotomy for unilateral disease, or median sternotomy or bilateral staged thoracotomies for bilateral metastases [19].

In addition to its potential survival benefit, a surgical approach to recurrent stage IV disease may be considerably safer for the patient. In the present study, procedure-related mortality was low (1/83, or 1.2%) for the 83 patients undergoing an attempted second complete metastasectomy for recurrent stage IV disease. This compares favorably with the significant morbidity associated with chemotherapy/biochemotherapy. Although several investigators have attempted to mitigate drug toxicity by altering dosing regimens [13,14], the toxicity associated with biochemotherapy is still significant. Thus, our treatment of choice for metastases to a single anatomic site is surgical resection — if all disease can be removed.

Recurrence of stage IV melanoma following complete metastasectomy could be the result of occult tumor deposits not detected by modern imaging techniques (computed tomography, magnetic resonance imaging, positron emission tomography) or dormant micrometastatic tumor awaiting the appropriate growth factors and angiogenic factors. Either etiology calls for an effective systemic adjuvant therapy following resection of all known metastases, but thus far no prospective randomized trial has demonstrated a survival benefit of postoperative systemic adjuvant therapy in stage IV melanoma patients rendered surgically free of disease. National Cancer Institute protocol NCI-G96-1089 (Principal Investigator: A. Bedikian) is investigating biochemotherapy as a postsurgical adjuvant in patients with regional melanoma (AJCC stage III); perhaps this also merits consideration in patients who have undergone complete resection of stage IV melanoma. A less toxic alternative is immunotherapy. Using active specific immunotherapy with an allogeneic polyvalent melanoma cell vaccine (CancerVax™), our group demonstrated improved survival in a cohort of stage IV melanoma patients [20], and we have therefore undertaken a Phase III randomized multicenter trial of Bocille Calmette-Guerin (BCG) plus CancerVax vs. BCG plus placebo as a systemic adjuvant therapy following complete resection of stage IV metastases (NCI protocol 1R01 CA76489-01A1; Principal Investigator: D.L. Morton) (Fig. 2).

We conclude that melanoma patients who develop recurrent stage IV disease following an initial complete metastasectomy should be considered for a second metastasectomy. An aggressive surgical resection should be performed if preoperative radiologic imaging and surgical exploration indicate that the tumor can be completely resected.

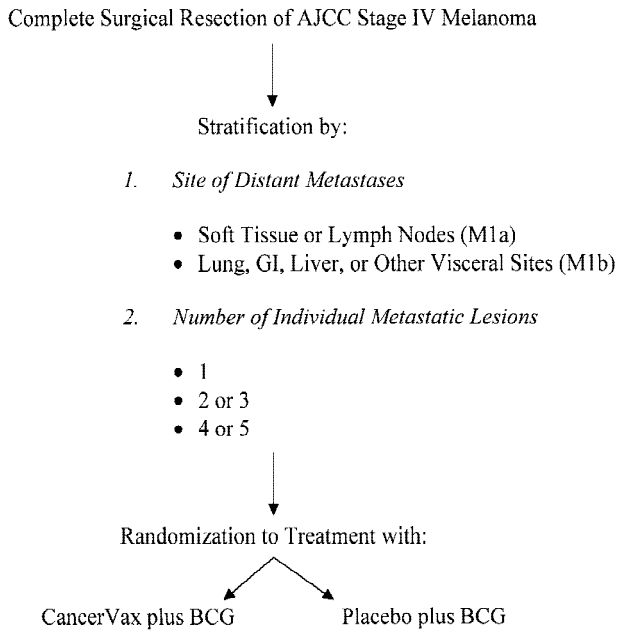

Fig. 2. Algorithm for a phase III multicenter, double-blind randomized trial of a polyvalent melanoma cell vaccine (CancerVax) plus Bacille Calmette-Guerin (BCG, an immune adjuvant) vs. placebo plus BCG in patients who have undergone complete surgical resection of AJCC stage IV melanoma.

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